Diffusion-weighted MRS and MRI : methods and neuro applications

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Summary and Conclusions

8.1 Summary

The main purposes of this thesis were (i) to investigate neuroanatomy *in vivo* with DW-MRS, (ii) to develop methodology to enable future clinical applications of the technique in human brain *in vivo*, and (iii) to characterize the microstructural deficit in neuropsychiatric systemic lupus erythematous (NPSLE) with DW-MRS and other microstructural tools such as DTI and MTI. The first part of the thesis, consisting of chapters 2 to 4, related to the first purpose, in which: (a) the link between diffusion properties of brain metabolites and the cellular morphology of the compartments that they are found in was investigated, (b) acquisition and post-processing protocols were evaluated and optimized, and (c) a new method was introduced to provide spatially resolved metabolite diffusion properties. In the second part of the thesis, two clinical research applications conducted on NPSLE were described (chapters 5 and 6), where disease-related microstructural changes were assessed by applying DTI together with two separate methods: MTI and DW-MRS.

In **Chapter 2**, the neuroanatomical correlate of metabolite diffusion properties was investigated within the context of their host compartment. DW-MRS was applied in a small VOI in the anterior body of the corpus callosum using a 7 Tesla MRI system. A new strategy was proposed for analyzing the DW-MRS data. The results of the study showed that metabolite diffusion calculated for tNAA, tCr and tCho reflects neuroanatomical features of the anterior body of the corpus callosum, highlighting the potential of DW-MRS to obtain compartment-specific information from human brain *in vivo*.

Chapter 3 presented an investigation of the reproducibility of DW-MRS and optimization of the acquisition scheme for *in vivo* human brain applications. For this purpose, DW-MRS and DTI data were obtained through five repeated scan sessions from six healthy volunteers. Three of these volunteers were scanned on a 3 Tesla MRI system and the remainder on a 7 Tesla MRI system in order to assess and compare the reproducibility and the reliability of metabolite diffusion values obtained at different magnetic field strengths. The inter-subject analysis showed that robust diffusivity results can be obtained at 3T and 7T with a lower variability for 7T scans. An investigation of optimal b-value scheme and number of averages showed that with an optimum acquisition scheme, it is possible to reduce the scan time for DWS to 10 minutes for 7T and 13 minutes for 3T with a variability of 8%. Power calculations showed that DW-MRS could provide reliable information to detect a 10% effect in case-control studies with 11-13 subjects per group (to obtain p-value < 0.05 and a power of 80%).

In **Chapter 4** , a new method, diffusion-weighted chemical shift imaging (DW-CSI) is introduced to obtain spatially-resolved metabolite diffusion properties. The feasibility of DW-CSI acquisition and processing schemes to measure metabolite diffusion from human brain was shown for the first time. Methodological developments that were implemented in this study enabled robust and reproducible results that are in line with the results from single volume DW-MRS experiments in the literature. Metabolite diffusion values calculated with DW-CSI were shown to relate to the underlying tissue gray and white matter decomposition.

Part two of the thesis, consisting of Chapters 5 and 6 related to clinical applications on NPSLE. In **Chapter 5** , DTI and MTI data were co-analyzed to investigate disease-related changes in the brain of the NPSLE patients. MTI changes observed in white matter of NPSLE patients were localized for the first time and were combined with the localized changes observed in DTI. Significantly lower MTR and FA and significantly higher AD,

RD and MD values were found in NPSLE patients compared to healthy controls. Most of these changes were observed in normal-appearing white matter of the brain. The changes observed with MTI and DTI metrics were only moderately co-localized suggesting that the underlying changes in DTI metrics are different than those observed by MTR. DTI metrics were found to be more sensitive to changes in the brains of active NPSLE patients compared to SLE patients and healthy controls, whereas MTI was sensitive to SLE-related changes, regardless of the presence of NP symptoms. Although informative, the combination of DTI and MTI still lacked the specificity needed to explain the source of these changes.

In **Chapter 6** , microstructural changes in the brains of SLE patients with a history of NPSLE were investigated by applying DW-MRS and DTI. The results indicated that intracellular alterations, and in particular changes in glia, significantly correlated with SLE activity. This is the first time in which such intracellular changes in the brain have been observed *in vivo* in relation to an autoimmune inflammatory disease. These findings suggested that diffusion properties of choline compounds and of total creatine are potentially unique markers for glial reactivity in response to inflammation.

8.2 Conclusions

DW-MRS can play a key role in understanding neurobiological mechanisms of diseases that affect the human brain. The specific changes that occur within neurons can be reflected as changes in the diffusivity of tNAA, whereas the changes in glial cells can cause pronounced changes in the diffusivities of tCr and tCho. This information combined with that obtained from DTI and other MRI tools can help elucidate various disease processes in the future. The studies presented in this thesis show the robustness and clinical relevance of microstructural information obtained via DW-MRS. The contributions of this thesis such as the optimized acquisition protocols for single volume (SV) DW-MRS, the robust DW-CSI and DW-MRS post-processing pipelines that comprise information from DTI, will all facilitate the applications of DW-MRS both for basic neuroscience research and clinical research studies and well as to increase the number of applications of DW-MRS in human brain *in vivo*.